FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: April 5, 1997

To: Mark Brunswick, Ph.D., Committee Chairman, HFM-555

From: Janice Brown, M.S., Committee Member, HFM-206

Through: Julia Gorman, Chief, Branch 1, Division of Establishment Licensing, HFM-206

Subject: Review of Biologics License Application (BLA) from IDEC Pharmaceuticals Corporation for the manufacture and formulation of rituximab also known as IDEC-C2B8 (PanThera™); Reference Number 97-0260

The subject of this submission is a shared manufacturing agreement between IDEC Pharmaceutical Corporation (IDEC) and Genentech, Inc. IDEC manufactures and formulates the active drug substance, rituximab, and Genentech fills, packages, and distributes the drug product.

I have separated my review into two sections, the first sections are questions related to the submission that can be addressed in an information request letter and/or during the pre-license inspection and the second section is a narrative of my review.

My review includes of an evaluation of the following sections submitted in the Chemistry, Manufacturing, and Control section of BLA: **Volume 2**, Sections D.1 and D.2; **Volume 3**, Sections II.A. Drug Substance, 1.a. and 1.b.1; **Volume 5**, Sections II A. Drug Substance, A.2. Manufacturing, A.3. Method of Manufacture, a.1-3, b., c.1, c.2.a.1-2, c.2.b.1-2; **Volume 9**, Section II A. Drug Substance, A.4.a-b, A.4.c.1.a-c, A.4.c.2.c-e; **Volume 11**, Section II.A.4.c.4.; **Volume 15**, Section II A. Drug Substance, A.7, Section II D. Environmental Assessment. After review of the submission, I have the following questions and comments.

(b)(4)

1. Volume 9, page 29 states that the cell free harvest material is typically held for [—] hours prior to loading onto a [——] column. Support for this hold period are the product characteristics for lot 102-010 that was held at the harvest stage for [—] hours. Volume 9, page 12 states that the bioburden action limit for the product held in the cell free receiving tank is >10CFU/mL, however, page 19 indicates

that lot 102-010 had a bioburden level of 0CFU/mL at this stage. Typically, validation studies in support of a hold period include three manufacturing lots to ensure results are reproducible over several manufacturing batches and can be supported by stability studies to ensure that the hold period did not adversely affect the stability profile of the product. Support for the hold period should include typical bioburden levels encountered in the product to include a "worst case" scenario. In this case I would recommend a bioburden challenge. Please review bioburden data from different manufacturing lots that can be used to support this hold period. In addition, the sponsor should submit data to include a worst case challenge to validate the hold period.

2. The cells are harvested from the [~~~] bioreactor and filtered into a cell free receiving tank. If the cell free bulk is not purified within 24 hours, the product is cooled to 2-8°C in the cell free receiving tank, otherwise product is held at ambient temperature. Volume 9, page 29, states (b)(4) that the bioburden action limit for the cell free bulk is 10 CFU/mL. The submission also states that the typical hold period is [~~~] hours prior to loading onto the [~~~~~] column. Please review the validation supporting the maximum length of time the cell free bulk may be held at 2-8°C and ambient temperatures. In addition, please clarify whether sampling is performed before or after the hold period.

3. IDEC experienced several mycoplasma and bacterial contamination events during the 1996 C2B8 campaign. IDEC submitted a summary of the contamination events to the Division of Establishment Licensing dated February 24, 1997. Page 12 of the summary report states that a total of [~] lots were produced during the 1996 C2B8 campaign. Four lots were positive for mycoplasma, lots 102-016, 102-018, 102-019, and 102-021 and three lots were discontinued due to bacterial contamination. During the pre-license inspection, a focus should be a review of their manufacturing history including their investigations and corrective actions.

4. Volume 5, pages 49-51 of the BLA summarize the 1996 IDEC C2B8 campaign. The summary indicates that [~] lots were (b)(4) produced, two lots were contaminated with Mycoplasma and three lots were contaminated with bacteria. The summary failed to identify that lot 102-019 was contaminated with Mycoplasma (they reported negative results) and omitted lots 102-001 and 102-021 from their summary. Throughout the CMC section of the BLA that I reviewed, lot 102-021 does not appear in the 1996 C2B8 campaign. The 1996 campaign started in mid July and the mycoplasma results for lot 102-021 were received on December 11, 1996, therefore, lot 102-021 must have been formulated at least 14-16 days earlier because the

test for Mycoplasma takes 14 days. During the pre-license inspection please review the following:

a. A possibility exists that other lots have been manufactured after lot 102-021 but were not reported. Both submissions stated that Genentech tested cells from the harvest stage of manufacture using the DNAF fluorescent method and culture for the detection of Mycoplasma along with vial testing. The Mycoplasma and viral testing results from both companies should be compared to determine if any under reporting or errors in reporting have occurred.

b. Special emphasis should be given to an evaluation of test methodology and reporting of test results from Genentech.

c. Volume 6, page 143 states that the initiation of a batch is defined as the inoculation of the [redacted] bioreactor and the completion of a batch is defined as the formulation of the bulk drug substance. Emphasis should be given to determine the number of contamination events (if any), prior to inoculation into the [redacted] bioreactor.

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d. Volume 5, page 48 states that gentamicin will be added to the cell culture media as a final prophylactic measure to prevent Mycoplasma contamination. Please review all their validation studies supporting the addition of gentamicin.

5. Volume 15, page 121 contains the stability data for the formulated bulk product. Both batches on stability contained [redacted] in the growth medium. [redacted] in the growth media. One of the two batches were tested in the actual container/closure, the [redacted] bag. Please clarify whether additional lots of C2B8 grown in [redacted] and gentamicin and stored in the [redacted] Bio-Process bag were included in the stability study.

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6. Volume 5, page 36 of the submission states that the manufacturing facility will be operated as a single product production facility. Page 9 of the February 1997 communication states that prior to the 1996 C2B8 campaign, IDEC clinical products [redacted] and contract manufacturing was also performed in this facility. Please clarify whether the manufacturing facility will be used for contract and/or clinical manufacturing.

7. Volume 5, page 48 of the submission states that two Working Cell Banks, [redacted] were produced from the Master Cell Bank [redacted] Page 48 of the

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submission also explains that both WCBs were fully characterized according to the agency's points-to-consider documents but did not state whether all tests passed the acceptance criteria for both working cell banks. Volume 5, page 206 of the submission describes the preparation of Working Cell Bank WCB [redacted] and states that this cell bank passed all the required tests, however, there was no mention as to the test results of [redacted] During the pre-license inspection, the test results for both WCB's [redacted] should be reviewed.

(b)(4)

8. The submission states that during cell bank preparation and freezing, cells are initially held at -70°C then transferred to liquid nitrogen for long term storage. Typically, most screw cap cryovials have a recommended temperature specification and cannot withstand temperatures colder than -70°C. Tubes stored outside the recommended temperature range, frequently lose integrity between the tube and closure. Additionally, upon thawing the tube body develop microfractures which also compromises the tube integrity and its contents. During the pre-license inspection, a review of the cryotube manufacturer's temperature specifications should be evaluated.

(b)(4)

9. Both compendial and non-compendial tests are performed for raw materials. Volume 5, page 56 of the submission states that identity test(s) are performed for the special reagents and materials, on an "as appropriate" basis. Please clarify if all raw materials are tested for identity. It is required [redacted] that for critical raw materials, the COA should be supplemented by verification of the vendors critical assay results using a validated in-house assay or those of a qualified contract laboratory. Critical components include chromatography resins (verified by protein capacity test and/or ligand identification test and/or backbone identity by Fourier transform infrared spectrometry (FT-IR)), serum, cell culture media (should be tested for bioburden, viruses, Mycoplasma, and enzymes, as appropriate).

10. Please review the acceptance criteria including the test(s) performed for the pre-sterilized [redacted] storage bags used to transport the drug substance to Genentech.

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11. Volume 5, page 24 of the submission states that released raw materials are transported from the warehouse on [redacted] to the [redacted] warehouse using an IDEC Pharmaceutical Corporation [redacted] Please clarify how temperature controlled materials (2-8°C and -20°C) are properly maintained during loading, unloading, and transit. In addition, please clarify how the temperature is monitored and verified routinely once materials arrive at the [redacted]

warehouse.

12. The submission states that integrity of the bioreactors are tested using a pressure hold test prior to sterilization. Please clarify if the bioreactor integrity is tested after sterilization and/or after completion of the production run.

13. The submission states that the gas filters on the bioreactors are post-sterilization integrity tested using a water pressure intrusion test. Please clarify if the filters are also tested after each production run to confirm bioreactor integrity.

(b)(4) 14. Volume 6, page 148 states that the Overhead Drive Spinner Flask (ODSF) is disconnected and transported to the Cell Culture Area, Room [redacted] Please clarify whether the integrity of the ODSF is tested, prior to inoculation into the [redacted] bioreactor and if the [redacted] bioreactor is tested for integrity prior to inoculation of the [redacted] bioreactor.

15. Volume 6, page 183 states that product tanks are equipped with a [redacted] vent and process filter, inlets, temperature indicator, pressure gauge, agitator, and manual diaphragm valves. Please clarify if these tanks are routinely or periodically tested for integrity.

16. Please clarify whether all aseptic connections were validated using a media challenge conducive for bacterial
(b)(4) growth. The aseptic connections include: (1) tubing connections from the [redacted] spinner flasks to the [redacted] ODSF; (2) filter sterilization of the culture medium into the bioreactor [redacted] filter assembly is connected to the [redacted] bioreactor and the connection steam sterilized); (3) withdrawal lines for sampling and harvesting from the ODSF; (4) the connection from the ODSF to the [redacted] bioreactor inoculum port; (5) sample bottle to the bioreactor (independent cycle for multiple samples;(6) the [redacted] filter assembly connection to the [redacted] bioreactors used to sterilize cell culture media.

17. Please review the following regarding equipment cleaning during the pre-license inspection:

a. Validation of the cleaning procedure should include the following: the frequency of routine or periodic testing
(b)(4) following the cleaning procedure, sampling procedure (final rinse, swabbing), residual detergent detection (Volume 15, page 163 state that the CIP agents are [redacted] a description of test methods evaluating residuals following the manual cleaning procedure, validation of the test methods, and frequency

of revalidation. If the cleaning procedure is manual, the firm should have validation demonstrating reproducibility and routine testing to ensure the validated process is maintained.

b. Volume 6, pages 149, 152, and 158 states that once the culture has been transferred or harvested, the bioreactors, the depth filtration assembly, and the micron filter are rinsed but not cleaned. The submission continues by stating that the CIP cycle is performed within three days after completion of the manufacturing batch. Although a rinse is performed, there may be residual protein in the bioreactor along with standing water. Additionally, water used to rinse the bioreactor may contain bioburden. Bioburden in standing water in a closed vessel with residual protein creates an environment conducive to the growth of microorganisms. The firm may perform a CIP procedure to remove microorganisms, however, if gram negative bacteria are present, endotoxins are also present. Endotoxin is extremely difficult to remove during cleaning, even with the use of caustic cleaning solutions. The firm should have supporting data demonstrating that the rinsed tanks do not support microbial growth during the three-day hold period (e.g., drying the tank after rinsing). In addition, validation of the CIP should parallel what occurs during actual use.

c. Following chromatography, the bulk is diluted and passed through a [—] micron filter into a dedicated stainless steel vessel. Volume 6, page 179 states that the micron filter housing, hoses and valves are chemically cleaned and sanitized. Please review the cleaning and sanitization validation for this procedure.

(b)(4)

d. Please review the cleaning validation for the following:
[

15 lines

]

(b)(4)

(b)(4) [3 lines]

18. Please review the sterilization validation for the following: [

(b)(4) 15 lines

]

19. In addition, please clarify the frequency of revalidation and the tests performed during these studies noted in questions 17 and 18.

20. Regarding the validation supporting the number of cycles the chromatography columns can be reused:

    a. Volume 9, page 45 states that the [———] column can be reused up to [—] times. The submission does not provide any supporting data demonstrating the number of times the column may be reused. Please review data supporting this claim. (b)(4)

    b. The submission states that the [———] may be used up to [-] cycles. Volume 9, page 46 provides data to support the number of cycles the column may be used. The product quality was comparable for cycle [———] using the [———] resin. No additional data was submitted to support [———] for the [———] column.

21. Please review the following computer/controller functions during the pre-license inspection:

    a. the controller that monitors and regulates the

    (b)(4)

    i. [———] bioreactors;

    ii. [———] column;

    iii. [—] column;

(b)(4) iv. [redacted] adsorption (if used);

v. Biowaste Collection System; and

vi. General Waste Collection System.

22. Regarding filter validation. Please review the following during the pre-license inspection:

a. [

10 lines

(b)(4)

]

b. [

6 lines

]

c. [

4 lines

]

(b)(4) d. [

4 lines

]

e. [

5 lines

]

23. Regarding validation of the sanitization effectiveness. For each of the following, please clarify their performance standard, challenge organisms, inoculum size, organic load (if appropriate), and time/temperature requirements:

a. Volume 5, page 19, states that equipment brought into the facility is surface sanitized with aqueous

disinfectant or 70% isopropyl alcohol. Please submit the validation studies demonstrating the disinfectant effectiveness of the disinfectant agent(s) and the 70% isopropyl alcohol. Please include an organic challenge, as appropriate.

(b)(4)

b. The submission states that the [ ] column is sanitized with [ ] however, no data supporting the validation of the sanitization procedure was included in the submission. Please review validation supporting this sanitization procedure.

c. After the product is concentrated by [ ] and [ ] Volume 6, page 172 states that a sanitization procedure is performed for the [ ] Please review the validation demonstration the sanitization effectiveness for [ ] minute exposure time for the [ ] apparatus.

(b)(4)

d. Volume 6, pages 175 and 177 states that the [ ] and the [ ] Module are sanitized using [ ] Again, no sanitization effectiveness data using [ ] was supplied.

e. Following chromatography, the bulk [ ] Volume 6, page 179 states that the [ ] filter housing, hoses and valves are chemically cleaned and sanitized, but validation details were not submitted.

f. Volume 6, page 157 states that the [ ] filtration apparatus is chemically cleaned and rinsed with WFI, however, the submission did not state whether the product contact surfaces are sanitized after the cleaning procedure has been completed.

(b)(4)

g. Volume 6, page 183 states that product tanks are equipped with a [ ] and process filter, [ ] valves. The tanks used for holding/receiving purified product and formulated product are cleaned sanitized or sterilized, however, no validation data was included in the submission.

24. Please describe the closure for the borosilicate glass bottles used to store culture and feed medium. Additionally, please submit validation data demonstrating the integrity of the closure and the glass bottles.

25. The submission states that compressed air is used to perform the following: test bioreactor(s) and tank integrity, pressurize bioreactor for cell culture transfer, pressurize transfer lines for product transfer. Please review the validation and the routine test program for the compressed air. Compressed air should be routinely tested for oil and moisture. If point of use sterilizing filters are used, viable and nonviable particulates need not be evaluated.

26. IDEC performs the seed preparation, cell culture processing, purification, and formulation. Volume 5, page 7 of the submission states that viral screening, MVM infectivity, and Mycoplasma release testing are performed by Genentech, Inc. During the pre-license inspection, please review the firms' audit procedures, specific attention should be focused on adequate personnel training, adequacy of standard operating procedures, and Quality Assurance oversight by IDEC.

27. Regarding the containers and closures

    a. Section II.A.7 - Appendix 8 (Volume 15, pages 1-119) includes data from the Manufacturer, [redacted] for the container closure system. These bags have been irradiated and are presumed to be sterile, however, data submitted in these sections does not support sterility of these containers. For example, Volume 15, page 28 includes bioburden testing for [redacted] bags. Bioburden levels ranged from 0-3 CFUs/bag. Pages 47 and 80 contain bioburden results ranging from 0-1 CFU/dL for ports, 0-8 CFU/dL for the base plate, 0 CFU/dL for the connectors, and no data was presented on the tubing. Please clarify how bioburden can be isolated from irradiated containers and associated components.

(b)(4)

    b. Volume 15, page 31 includes a summary of the testing performed on the [redacted] used for the [redacted] bag. The summary states that the [redacted] was irradiated at [redacted] which exceeds the recommended dose for these containers. Volume 15, page 10 states that the materials that comprise the [redacted] Containers tolerate up to [redacted] with no loss of integrity. Please clarify why these containers and assemblies were irradiated outside the manufacturer's recommendations.

(b)(4)

    c. The schematic supplied in Appendix A.7-8, pages 117-119 illustrates the packaging configurations for the [redacted] and [redacted] Containers, the [redacted] and [redacted] media bags. During the pre-license inspection, please observe how the base plate, port(s), and fitting

(b)(4)

are used in the assembly of the transport container.

d. Please clarify how the integrity of the [——] [————] Bags are verified, after arrival at Genentech.

(b)(4)

e. In Appendix D-3 of the Environmental Assessment (Volume 15, page 166) lists buffer hold bags under materials that would be disposed of as solid waste. Please clarify whether buffers are also stored in [————] bags. If so, please review container/closure studies to include: validated hold time(s), raw material acceptance and if partial volumes can be removed, the firm should also have validation studies supporting this procedure, to include the number of times the container can be opened and closed.

28. Please review the shipping validation study of the bulk drug substance from IDEC Pharmaceutical Corporation in San Diego to Genentech, Inc. in San Francisco, California. The shipping validation study should describe the following: temperature monitoring and documentation during transit, vibrational impact on the closure, and validation of the transport vehicle. We recommend that shipping validation studies include a "worst case" scenario using actual conditions or a simulation of actual conditions, for example, vibrational impact on the closure and temperature and time effects on the drug product. Please review the SOP describing shipping operations developed from the validation study to include routine monitoring in the hottest and coldest location(s) in the transit vehicle. In addition, the firm should have specific procedures addressing product impact in the event of an excursion during transit (e.g., truck breakdown).

29. Regarding the HVAC system and environmental monitoring:

a. During the pre-license inspection, the following items should be evaluated: (re)validation of the HVAC system including system capacities for supply and return air and exhaust; HEPA filter certification frequency and tests performed (air velocity); environmental monitoring for both viable and nonviable particulates; monitoring of differential pressures, air temperatures, and humidity. Additionally, the [————] biological safety cabinets, surface and personnel monitoring should be included in the review.

(b)(4)

b. Please review the HEPA filter certification and ensure that they are certified routinely.

c. The submission states that culture and feed medium is sterile filtered into glass bottles in a [———] BSC. Please clarify if any monitoring is performed during this operation.

(b)(4)

d. Volume 5, page 15, of the submission includes a HVAC exhaust/intake diagram that indicates air intake is next to 8 exhaust outlets on the roof, including the [———] exhaust. During the pre-license inspection, the roof top exhausts should be examined to ensure that incoming air is not compromised by the exhausts of fume hoods and equipment.

30. Regarding the water system(s):

a. Please review the validation for the water system, to include the following: support for the routine monitoring schedule of the pre-treatment system; a determination of the total number of use points and monitoring frequency for the water system and the clean steam points-of-use.

b. We recommend that the WFI system be routinely monitored for microbial and endotoxin levels on a daily basis, rotating the points of use so that each point is monitored weekly. Conductivity and TOC measurements should also be performed at the worst case position (e.g., return after the last use point). Further, the submission did not include a statement regarding whether the water system(s) has been validated (increased monitoring frequency). Additionally, a review of the firm's investigation in the event of excursion(s) should be performed.

c. Please review the validation and routine monitoring for clean steam. We recommend that for critical operations that clean steam is monitored twice a month and monthly for non-critical operations. Further, clean steam should meet the U.S.P. requirements for WFI.

31. Regarding the Biowaste Containment and General Waste Collection Systems. Please review the following during the pre-license inspection.

(b)(4)

a. Volume 15, page 142 of the submission states that waste is held at [———] Please review the validation for waste decontamination cycle and verify that the performance standards have been met.

b. Verify that the tank volume for the biowaste containment collection, the general waste collection, and the neutralization tank can hold the appropriate volume

during actual operations.

c. Verify that the computer controlled functions have been validated.

d. Volume 5, page 143 states that the sump pump, biowaste collection tank, and the neutralization tank are equipped with alarms. Please clarify whether these are local alarms or whether they are connected to a central monitoring system.

e. Please clarify whether all drains leading to the biowaste collection tank and general waste system are equipped with backflow preventors or an alternate method to prevent backflow.

32. Regarding the Environmental Assessment. Please review the following during the pre-license inspection.

a. how is a failed lot of drug substance or formulated drug substance disposed.

b. has this possibility been included in the amount expected to be discharged into the publicly owned treatment works listed in Appendix D-2, Volume 15, page 165.

c. verify that IDEC has the following for the company used in the disposal of the drug substance: license or permit number, EPA/or equivalent ID number (if any), license or permit expiration date, and issuing agent.

(b)(4)

THIS SECTION WAS DETERMINED TO BE NOT RELEASABLE

18 pages